



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: JOHN F.T. CONROY, M.E. POWER, AND P.M. NORRIS

Serial No. : 09/785,188

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Examiner: David M. Naff

Title : SOL-GEL BIOMATERIAL IMMOBILIZATION

Mail Stop Appeal Brief - Patents

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

SUPPLEMENTAL REPLY BRIEF

Applicant submits this Supplemental Reply Brief responsive to the Examiner's Answer dated March 29, 2006. No deficiency in the Reply Brief filed May 26, 2005 has been identified and the Reply Brief filed May 26, 2005 is understood to be fully responsive to the Examiner's Answer dated March 29, 2006. However, the paragraph headings in the present Supplemental Reply Brief that identify page and line numbers have been changed to correspond with the Examiner's Answer dated March 29, 2006.

At page 5, line 18-23: In arguing that the rejection of claims 26 and 29 as obvious over Uo and Hino should be maintained, the Examiner's Answer contends that it would have been obvious to substitute vegetative yeast cells for the yeast spores found in Uo's gels "as suggested by Hino et al."

Hino suggests nothing of the sort. Hino makes no mention of vegetative yeast cells whatsoever. A rejection that is based on the use of vegetative cells is not based on the scope and

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content of Uo and Hino, but rather on a speculative combination of elements not found in either reference.

At page 5, line 23- page 6, line 9: In arguing that the rejection of claims 26 and 29 as obvious over Uo and Hino should be maintained, the Examiner's Answer contends that using vegetative cells in Uo's matrices would have been expected to simplify immobilization. In particular, the Answer contends that if vegetative cells were immobilized directly, they would not have to be converted to spores prior to immobilization and then back to the vegetative state for use. As best understood, this contention is to be a motivation for combining Uo and Hino.

Rather than providing a motivation for combining Uo and Hino, this contention further illustrates that one of ordinary skill would not immobilize vegetative cells in Uo's matrices with a reasonable expectation of success. In particular, under the logic of this contention, Uo went out of his way to avoid immobilizing vegetative cells. In doing so, he intentionally performed additional steps and complicated his immobilization process. Despite the urgings of the Examiner's Answer to the contrary, Uo explicitly identifies why he immobilized yeast spores. Namely, according to Section 2.2 of Uo, page 427, yeast spores were immobilized for their durability to organic solvents.

The Examiner's Answer now attempts to discard this express teaching of Uo regarding the desirability of yeast spore immobilants. *The Examiner's Answer assumes that it knows how to immobilize cells better than Uo himself*, dismissing Uo's intentional selection of yeast spores as unduly complicated. No basis founded in the art of record for this "obvious" improvement to Uo's process is presented. Rather, the Examiner's Answer bases an obviousness rejection on the

assumption that Uo is intentionally and unduly complicating his immobilization process without any justification for the assumption founded in the prior art.

At page 6, line 6-9 and page 9, lines 6-20: In arguing that the rejection of claims 26 and 29 as obvious over Uo and Hino should be maintained, the Examiner's Answer contends that the claims are deficient for not requiring that immobilized cells have a certain amount of activity after immobilization.

However, Applicant submits that there is no motivation to combine Uo and Hino without the immobilized cells having a certain amount of activity. The rejections of claims 26 and 29 are obviousness rejections under 35 U.S.C. § 103(a). Some motivation to combine the references must be present to establish a *prima facie* case of obviousness. *If the combination of Uo and Hino does not result in immobilized cells having a certain amount of activity, then there is no motivation for one of ordinary skill to combine Uo and Hino in the manner suggested.* In particular, there is no reason to believe that one of ordinary skill would select Uo's gelation solution to inactivate Hino's immobilants in a solid matrix.

Further, it is self-evident that both Uo and Hino expressly teach away from inactivating immobilants. Forming a gel with immobilants that lack a certain level of activity directly contradicts the teachings of both Uo and Hino. Therefore, as a "useful general rule," Uo and Hino cannot serve to create a *prima facie* case of obviousness where inactivated immobilants result from the combination. No reason for discarding this useful general rule has been provided.

At page 6, line 22– page 7, line 3: In arguing that the rejection of claims 26 and 29 as obvious over Uo and Hino should be maintained, the Examiner's Answer contends that it is

within the level of ordinary skill in the art to exchange cell durability for simplification of the immobilization process.

The fact that one of ordinary skill in the art is *capable* of exchanging cell durability for simplification of the immobilization process is tangential to the issue of whether or not a *prima facie* case of obviousness has been established.

Rather, a fundamental issue is whether or not one of ordinary skill would be *motivated* to exchange cell durability for simplification of the immobilization process. Uo and Hino clearly teach away from the inactivation of immobilants, and Uo leads away from the exact combination proposed by the Examiner's answer. Block at least suggests that one of ordinary skill would not have a reasonable expectation of success with the combination.

Nevertheless, the Examiner's answer insists on finding a motivation that disregards every reference of record. Absent some basis founded in the prior art that one of ordinary skill would indeed find the immobilization of inactivated immobilants attractive, the rejection cannot be maintained.

At page 7, line 7-12: In arguing that the rejection of claim 28 as obvious over Uo and Hino should be maintained, the Examiner's Answer contends that it would have been obvious to substitute bacterial spores for the yeast spores found in Uo's gels.

Neither Uo nor Hino make any mention of bacterial spores whatsoever. A rejection that is based on bacterial spores is not based on the scope and content of Uo and Hino, but rather on a speculative combination of elements not found in either reference.

At page 9, line 21- page 10, line 6: Given that both claims 26 and 29 require macroporous gels, in arguing that the rejections of claims 26 and 29 as obvious over Uo and Hino should be maintained, the Examiner's Answer contends that Hino suggests that a macroporous silica gel like Uo's can be obtained with an acceptable level of inactivation. At page 10, line 14-19, the Examiner's Answer contends that it would be obvious to omit methanol from Uo's process for immobilizing cells and yet a macroporous gel would still be obtained.

These contentions represent nothing more than unsupported armchair chemistry. A macroporous gel like Uo's without methanol is neither described nor suggested by Uo. A rejection that is based on a macroporous gel without methanol is not based on the scope and content of Uo and Hino, but rather on a speculative combination of elements not found within the scope and content of the references.

Further, every one of Hino's gels that immobilizes cells is explicitly excluded from being macroporous. Please see the Appeal Brief for a discussion of this point. Hino thus does not suggest that macroporous silica gels with an acceptable level of inactivation can be obtained.

Further, every recipe for macroporous silica gels in the art of record (including Uo's) requires toxic gelation conditions. Please see the paragraph bridging pages 9-10 of the Appeal Brief. Thus, the scope and content of the prior art suggests the exact opposite conclusion, namely, that macroporous silica gel like Uo's cannot be obtained without an unacceptable level of inactivation.

An obviousness rejection must be based on the scope and content of the prior art. The continued departure of the rejections from what is actually described in the art and reliance upon what the Examiner's Answer feels is obvious or possible is erroneous. *In re Lee*, 277 F.3d 1338 (Fed. Cir. 2002).

At page 10, line 16 – page 11, line 1: In arguing that the rejections of claims 26 and 29 as obvious over Uo and Hino should be maintained, the Examiner's Answer contends that Uo does not expose yeast spores to gelation solution for one day. In particular, the Examiner's Answer contends that after gelation, the spores are not exposed to gelation solution.

While agreeing with the assertion that Uo's yeast spores are not exposed to *pure* gelation solution for over one day, Applicant respectfully disagrees with the contention that, after gelation, the spores are no longer exposed to gelation solution. In Uo and every other reference of record, there is no instantaneous removal of the gelation solution from the pores of a gel after gelation. For example, at col. 12, line 2-6, Hino describes that the liquid component of lyogels is to be removed from the lyogels by ventilation drying to produce xerogels.

Uo's yeast spore are thus exposed to pure gelation solution during mixing, during the gelation reaction, and during any aging of the gel after gelation. Once gelation and any aging is complete, an alternative method called solvent exchange can be used to exchange the gelation solution with another solution. Uo uses such a solvent exchange process when he describes that the gels are crushed and soaked in sterilized water for one day at room temperature. During this day, the sterilized water penetrates the pores of the gel, gradually diluting the gelation solution in the pores until a uniform distribution of the mixture of sterilized water and gelation solution remains.

Thus applicant submits that Uo's yeast spores are exposed to pure gelation solution during mixing, during the gelation reaction, and during any aging of the gel after gelation. Uo's yeast spores are exposed to increasingly-diluted gelation solution during the day-long solvent exchange.

At page 11, line 1-19: In arguing that the rejections of claims 26 and 29 as obvious over Uo and Hino should be maintained, the Examiner's Answer speculates, without support, on a number of points. Together, these points amount to an assertion that Applicant has not proven that Uo's gelation solutions are toxic to Hino's immobilants. In particular, the Examiner's Answer speculates that TMOS and PEG *could* lessen the microbicidal affect of Uo's gelation solutions beyond that of otherwise pure methanol/water mixtures, and that the 45-55 Vol.% methanol in Uo's gelation solutions *could* be substantially less toxic than the 65 Vol.% methanol disclosed as toxic to *Staphylococcus aureus* and *Escherichia coli* in under 1 minute.

As to the gist of the unsupported speculation (i.e., that Applicant has not proven that Uo's gelation solutions are toxic to Hino's immobilants), it is well established that the burden of establishing a *prima facie* case of obviousness lies with the Office. Applicant is therefore not required to prove, at any evidentiary standard, that a particular combination proposed by the Office will not work. Rather, the Office is required to establish that one of ordinary skill would be motivated to carry out a proposed combination with a reasonable expectation of success.

That Uo, Hino, and Block at least suggest that one of ordinary skill would not have a reasonable expectation of success with the proposed combination does nothing to remove this burden from the Office. Rather, these references *must be considered* by the Office when attempting to establish the expectations of one of ordinary skill. The Office cannot dispense with these references simply by arguing that Applicant has not met an evidentiary burden of proving that a proposed combination will not, in fact, work. Rather, the Office must establish that one of ordinary skill would have a reasonable expectation of success with the proposed combination.

Turning to the individual points, the unsupported speculation that TMOS and PEG *could* lessen the microbicidal affect of Uo's gelation solutions and that the 45-55 Vol.% methanol in Uo's gelation solutions *could* be substantially less toxic than the 65 Vol.% methanol insufficient to establish that one of ordinary skill would reasonably expect success with the proposed combination. Perhaps if the Office could establish that the presence of TMOS and PEG would in fact lessen the microbicidal affect of Uo's gelation solutions beyond that of otherwise pure methanol/water mixtures (and overcome the express teaching of Uo to the contrary), one of ordinary skill might have been provided with a reasonable expectation of success. Perhaps if the Office could establish that 45-55 Vol.% methanol is in fact substantially less toxic than the 65 Vol.% methanol (and overcome the express teaching of Uo to the contrary), one of ordinary skill might have been provided with a reasonable expectation of success. However, no such showing has been made and a prima facie case of obviousness has not been established.

At page 11, line 20 – page 12, line 21 and page 13, line 8-12: In arguing that the rejections of claims 26 and 29 as obvious over Uo and Hino should be maintained, the Examiner's Answer contends that Hino's solvent casting in isopropanol of gels that retain 61% of their activity is evidence that Hino's vegetative cells can be contacted with Uo's methanol and retain their activity. The Examiner's Answer thus contends that Hino's cells are exceptions to the general susceptibility of vegetative cells to alcohols investigated over centuries and described in Block.

Applicant respectfully disagrees. Hino's solvent casting involves the extrusion of Hino's cell-containing gelation solutions into isopropanol. As the solutions contact the isopropanol, they gel, retaining the gelation solution in their pores. Once again, there is no instantaneous

removal of the gelation solution from the pores of a gel after gelation. Normally, if the gels are allowed to soak in the casting solution (here, isopropanol), the casting solution will penetrate the gel over time as it solvent exchanges with the gelation solution. However, Hino goes out of his way to avoid allowing isopropanol to reach the interior of the gel. In particular, Hino freeze dries the cast gels immediately. Such a freeze drying of the gels freezes the solvents, stopping the solvent exchange and allowing the cells on the interior of the gel to remain in contact with gelation solution.

Thus, Hino also teaches that contact between cells and isopropanol is to be limited, and that even contact limited by immediate freeze drying inactivates cells. This is not surprising given the teachings regarding the toxicity of isopropanol found in Block cited in the Appeal Brief. Hino's cells thus are not exceptions to the general susceptibility of vegetative cells to alcohols described in Block.

At page 13, line 2-3: In arguing that the rejections of claims 26 and 29 as obvious over Uo and Hino should be maintained, the Examiner's Answer contends that it is Uo's PEG and not Uo's methanol that forms macropores in Uo's gels.

There is no support for this contention founded in the prior art. Indeed, contrary examples can be found. For example, Hino uses PEG and yet the majority of his gels are expressly precluded from including macropores. There is nothing to suggest that Uo's and Hino's chemistry is as simplistic as "PEG forms macropores, methanol doesn't."

Moreover, this contention ignores the other references of record in the application. Every recipe for macroporous silica gels (including Uo's) requires toxic gelation conditions. The

Examiner's answer improperly disregards these references and instead relies upon unsupported speculation (i.e., "Uo's PEG forms macropores, Uo's methanol doesn't").

At page 13, line 6-8: In arguing that the rejections of claims 26 and 29 as obvious over Uo and Hino should be maintained, the Examiner's Answer contends that "there is inadequate evidence to establish that the methanol of Uo et al. is critical to obtaining macropores."

However Uo neither describes nor suggests a methanol-free macroporous recipe. A rejection that is based on a speculative modification of Uo's macroporous recipe to exclude methanol is not based on the scope and content of Uo and Hino, but rather on a speculative combination of elements not found in Uo and Hino.

Further, Applicant is no burden to make this proof. The burden of establishing a *prima facie* of obviousness lies with the Office. The Office cannot dispense with this burden simply by arguing that Applicant has not met an evidentiary burden of proving that a proposed combination will not, in fact, work.

At page 15, line 2-3: In arguing that the rejection of claim 28 as obvious over Uo and Hino should be maintained, the Examiner's Answer contends that there is no "substantial difference" between gels containing macropores and gels without macropores.

Applicant respectfully submits that any reading of an express limitation out of the claims during examination is improper. Further, this statement is contradicted by the references of record such as Kajihara and Nakanishi that intentionally develop macroporous recipes.

At page 15, line 11-13: In arguing that the rejection of claim 28 as obvious over Uo and Hino should be maintained, the Examiner's Answer is understood to contend that since Uo does not investigate the experimental relationship between pore size and methanol content that methanol can be eliminated from Uo's gelation solution.

Applicant respectfully disagrees. The mere fact that Uo did or did not chose to investigate the dependence of pore size on an experimental variable does not suggest that the uninvestigated variable can be eliminated. For example, Uo also did not investigate the dependence of pore size on catalyst concentration, precursor concentration, temperature, and time. By the logic of the Examiner's Answer, these variables could also be "eliminated" without any effect on pore size.

Once again, a rejection must be based on the scope and content of the prior art. Uo's gelation solution absent methanol is not found in the cited references. A rejection cannot be based on unsupported armchair chemistry.

At page 16, line 4-7: In arguing that the rejection of claim 15 as obvious over Uo, Hino, Klein, and Rao should be maintained, the Examiner's Answer is understood to contend that since Uo's robust yeast spores can be immobilized in 45-55 Vol.% methanol solutions, one of ordinary skill would be motivated to immobilize Uo's yeast spores in an approximately 65 Vol.% ethanol solution with increased toxicity, increased temperature, and an increased concentration of organic solvent. **At page 16, line 11-21,** the Examiner's Answer contends that one of ordinary skill would be motivated to ignore the increased toxicity, increased temperature, and an increased concentration of organic solvents so as to achieve more complete hydrolysis and condensation, an increased rate of hydrolysis, and an increased surface area.

These contentions ignore the requirement that the motivation to combine must have a reasonable expectation of success. Even if one assumes that more complete hydrolysis and condensation, an increased rate of hydrolysis, and an increased surface area are factors that would motivate one of ordinary skill to deviate from the ratios of moles water to moles hydroxyl metallate described in Uo and Hino, the use of the increased hydrolysis ratios must nevertheless provide a reasonable expectation of success.

The reasonable expectation of success is an element of a *prima facie* case of obviousness and the Office bears the burden of proof that the expectation is reasonable. Bald speculation that Uo's yeast spores would be expected to be resistant to gelation solutions with increased toxicity is insufficient. This expectation of success must be founded in the teachings of the prior art and not unsupported conclusions or an assertion that an evidentiary burden of proof away from the combination has not been met by the Applicant.

Further, Applicant has provided evidence that one of ordinary skill would expect nothing but increased inactivation with the proposed combination. Both Hino and Uo teach away from the inactivation of immobilants, as a general rule disqualifying their use as references to establish the proposed combination.

At page 16, line 7-11: In arguing that the rejection of claim 15 as obvious over Uo, Hino, Klein, and Rao should be maintained, the Examiner's Answer contends that it would be obvious to use a sol with a reduced amount of solvent so as to not to kill an undue number of cells.

None of the cited references describe or suggest a sol with the reduced amount of solvent suggested by the Examiner's Answer. A rejection that is based on a sol with the reduced amount

of solvent is not based on the scope and content of the prior art, but rather on a speculative combination of elements.

Further, claim 15 is directed to a sol containing a ratio of 25 or more moles water for each mole hydroxyl metallate. Assuming that the Examiner's Answer is not contending that the amount of aqueous solvent should be reduced (e.g., outside the claimed range), the Examiner's Answer is understood to contend that the amount of organic solvent should be reduced.

However, the only reference that discusses a ratio of water/hydroxyl metallate within the claimed range (i.e., Klein), describes that additional ethanol is necessary to permit solubility of the increased water in the sol solution. *See Klein, page 34, last sentence of the second paragraph.*

The Examiner's Answer has provided no guidance as to why or how this teaching is to be ignored. Not only does the Examiner's Answer propose a combination that directly contradicts the express teachings of Klein, it offers no guidance as to how the physical reality of insolubility of solvents is to be overcome. *The Examiner's Answer assumes that it knows how to handle high hydrolysis ratios better than the references of record* and dismissed their express teachings as unnecessary. Moreover, the constraints of physical reality identified in Klein are ignored by the Examiner's Answer in forming the speculative combination of elements.

At page 16, line 11-13: In arguing that the rejection of claim 15 as obvious over Uo, Hino, Klein, and Rao should be maintained, the Examiner's Answer contends that that the claims are deficient for not requiring that immobilized cells have a certain amount of activity after immobilization.

Applicant submits that there is no motivation to combine Uo, Hino, Klein, and Rao without the immobilants having a certain amount of activity. In particular, there is no reason to

believe that one of ordinary skill would select Klein's gelation solution to inactivate Hino's or Uo's immobilants.

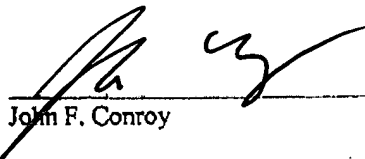
Moreover, it is self-evident that both Uo and Hino expressly teach away from inactivating immobilants. Therefore, as a "useful general rule," Uo and Hino cannot serve to create a *prima facie* case of obviousness where inactivated immobilants result from the combination. No reason for discarding this useful general rule has been provided.

For these reasons, and the reasons stated in the Appeal Brief, Applicant submits that the final rejection should be reversed.

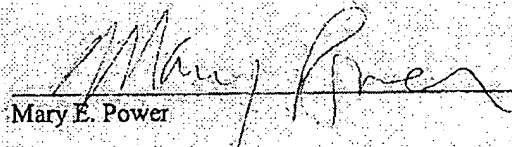
No fee is believed to be due.

Respectfully submitted,

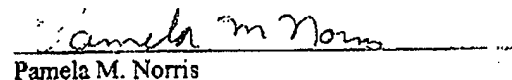
Date: May 30, 2006


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